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(19) (CA) **APPLICATION FOR CANADIAN PATENT** (12)

(54) Metronidazole Gel

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ABSTRACT

A topical composition for the treatment of rosacea and acne comprising:

(a) an effective amount of metronidazole or salt thereof;

(b) an effective amount of at least one sunscreen compatible with said metronidazole;

(c) a substantially alcoholic base as a vehicle.

TITLE OF INVENTION

Gel suitable for use in the treatment of rosacea and acne.

FIELD OF INVENTION

This invention relates to the treatment of rosacea and acne. In some embodiments this invention also finds application not only to the topical treatment of the skin due to a disease including rosacea, but also to diseases or conditions like erythemia, telangiectasia and inflammatory lesions, and the reduction of papule and pustule count as well.

This invention also relates to compositions preferably comprising metronidazole suitable for use in such treatments, the use of such formulations, the use of metronidazole and methods of carrying out such treatments.

BACKGROUND OF THE INVENTION

Rosacea is a chronic, dermatologic disease (inflammatory disorder) characterized by redness and telangiectasia of the face and punctuated by episodes of inflammation and recurrent crops of papules and pustules, and swelling as well. The pathogenesis (etiology) is unknown. Therapy usually involves administration of an oral antibiotic. Metronidazole has been administered orally and has been shown to be as effective as tetracycline in the treatment of rosacea.

However, concerns over possible toxicity associated with long term therapy prompted the development of topical formulations such as 1% cream, 0.75% water based gel, and even a 5% topical suspension.

For example, Vehicle Effect on Topical Drug Delivery Mollgaard et al. Acta. Pharm. Svec. Vol. 20, No. 6, 1983, purports to teach on pages 448-450, a Metronidazole carbopol aqueous gel which contains propylene glycol.

French Patent Publication No. 2,558,058, published on July 19, 1985, purports to teach on pages 3, 4, and 5, the use of Metronidazole in topical form, together with other ingredients in the treatment of acne. Pages 7 and 8 thereof purports to teach several types of bases which may be incorporated with Metronidazole, i.e. "One type of support may for example be constituted principally by the combination of 20 to 70% by volume of ethyl alcohol, the balance being found by water, glycerol, a polyol such as ethylene glycol, propylene glycol or their oxyethylene homologues alone in mixture:

The publication also provides:

> "In one preferred embodiment of the invention, the base is constituted by an 'équipondéral' mixture of ethyl alcohol and polyethylene glycol.
>
> It can also be equally associated with in small quantities, less than 10% of the total composition, ketones such as methylisobutyl ketone, alcohol esters like ethyl acetate as ethers like dimethoxymethane, which permits contribution of the known effect without causing any disagreeable effects to the skin.
>
> Furthermore, the dermatological compositions may contain other additions such as preservatives, perfumes, colouring agents, as would be expected in formulations of such compositions.

The dermatological compositions for external topical application can be introduced in the form of solutions, lotions, gels or creams. The solutions, gels or lotions may be conditioned in the classical manners in the form of flakes, aerosols or ampoules".

U.S. Patent 4,247.547, issued on January 27, 1981, purports to teach the use of hydroxy propyl cellulose as a gelling agent (column 4, line 12-13) and also the use of an acidic carboxy polymer, i.e. carbopol 940 as a gelling agent (column 4, line 14-15). It also purports to teach the use of an organic solvent in a gel formulation i.e. ethanol (absolute or 95% by volume ethyl alcohol), isopropanol, propylene glycol and combination thereof in a gel formulation for treating acne.

U.S. Patent 3,883.661, issued on May 13, 1975, purports to teach the use of hydrous or anhydrous gels with carbopols as gelling agents in the use with fatty acid amides in the treatment of acne.

The article entitled Metronidazole Suspension Applied Topically for Rosacea British Journal of Dermatology (1084) III, 499-502 purports to teach the use of metronidazole in a suspension for topical skin application in the treatment of rosacea.

Döring, H.F., et al., Z. Hautkr., Vol. 58, No. 3, pp 141-155 (1983) purports to teach the use of Metronidazole in the treatment of rosacea.

However, none of these formulations took into account that the sun, among other environmental factors like the wind or cold, could produce a dermal dystrophy in inherently susceptible individuals which could be the source of the symptoms observed in rosacea (see Marks et al, Rosacea and Perioral Dermatitis

from: Textbook of Dermatology 4th ed. by Rooks et al 1986; Chapter 40: 1605-1611). Several papers report that patients with rosacea complained that exposure to sun made their condition worse.

Since it is well established that sunlight makes rosacea worse, it would be beneficial to patients with rosacea to apply sunscreens to block the UV radiation from damaging the skin further by exacerbating rosacea.

It is therefore an object of the invention to provide a topical composition for the treatment of rosacea which includes sunscreens to block UV radiation from damaging the skin further, preferably the sunscreen blocks UV-A and UV-B radiation.

It is also another object of the invention to provide a method of treating rosacea where said method of treatment also includes a sunscreen to block radiation.

It is also another object of the invention to provide a composition that is effective against telangiectasia, and against papules and pustules.

It is also another object of the invention to provide a composition in one embodiment which is substantially in an alcohol base gel exhibiting bactericidal qualities.

It is a further object of the invention to provide such composition which because of the use of an alcohol base, minimizes any stinging effect and preferably substantially has no stinging effect.

Further and other objects and benefits of the invention will be realized by those skilled in the art from the disclosure and the accompanying claims.

SUMMARY OF THE INVENTION

Thus, according to one aspect of the invention there is provided a topical composition for the treatment of rosacea and acne comprising:

(a) an effective amount of metronidazole or salt thereof;

(b) an effective amount of at least one sunscreen compatible with said metronidazole; and

(c) a suitable vehicle, preferably a substantially alcoholic base.

According to another aspect of the invention there is provided a topical composition suitable for the treatment of rosacea and acne comprising:

(a) an effective amount of an antibiotic; preferably metronidazole

(b) an effective amount of a sunscreen; preferably selected from the group consisting of octyl methoxycinnamate and butyl methoxydibenzoyl methane

(c) an effective amount of an emollient; preferably selected from the group consisting of dioctyl maleate and isoarachidyl neopentanoate

(d) an effective amount of a lubricant; preferably cyclomethicone

(e) an effective amount of a gelling agent; preferably hydroxypropyl cellulose, and

(f) an effective amount of a pharmaceutically acceptable diluent or carrier for the above, preferably isopropyl alcohol 99% USP.

According to yet another aspect of the invention there is provided a substantially topical gel composition for the treatment of rosacea comprising:

(a) an effective non-toxic amount of an antibiotic; preferably metronidazole

(b) an effective non-toxic amount of a sunscreen; preferably selected from the group consiting of octyl methoxy cinnamate and butyl methoxydibenzoyl methane

(c) an effective non-toxic amount of an emollient; preferably selected from the group consisting of dioctyl maleate and isoarachidyl neopentanoate

(d) an effective non-toxic amount of a lubricant; preferably cyclomethicone

(e) an effective non-toxic amount of a gelling agent; preferably hydroxypropyl cellulose, and

(f) an effective amount of a pharmaceutically acceptable diluent or carrier; preferably isopropyl alcohol 99% USP. .

According to yet another aspect of the invention there is provided you missed (in one embodiment) a topical composition for the treatment of rosacea, erythemia, telangiectasia, and inflammatory lesions associated with rosacea, erythemia, telangiectasia, said topical composition comprising:

a) isopropyl alcohol 99% USP in the amount of about 72.5% - 71.5% w/w;

b) purified water USP in the amount of about 4.0% w/w;

c) dioctyl maleate MFR in the amount of about 4.85%-5.5% w/w;

d) cyclomethicone NF in the amount of about 2.91%-3.5% w/w,

e) Octyl Methoxycinnamate in the amount of about 7.5%-8.0% w/w;

f) isoarachidyl neopentanoate MFR in the amount of about 3.75%-4.5% w/w;

g) metronidazole USP in the amount of about 0.50% - 1.50% w/w;

h) Butyl Methoxydibenzoyl methane in the amount of about 2.0%-2.2% w/w; and

i) hydroxypropyl cellulose NF in the amount of about 1.2%-1.5% w/w, or pharmaceutically acceptable chemical equivalents of a)-i).

According to yet another aspect of the invention there is provided in one embodiment a composition for the treatment of rosacea and acne comprising:

(a) an effective amount of isopropyl alcohol 99% USP

(b) an effective amount of purified water USP

(c) an effective amount of dioctyl maleate MFR

(d) an effective amount of cyclomethicone NF

(e) an effective amount of Octyl Methoxycinnamate

(f) an effective amount of Isoarachidyl neopentanoate MFR

(g) an effective amount of metronidazole USP

(h) an effective amount of Butyl Methoxybenzoyl methane MFR and

(i) an effective amount of hydroxypropyl cellulose NF, or pharmaceutically acceptable equivalents of each of (a) - (i)

According to yet another aspect of the invention there is provided a method of treating rosacea and acne comprising the topical application of an effective amount of metronidazole in combination with: an effective amount of at least one sunscreen compatible with said metronidazole, preferably selected from the group consisting of octyl methoxycinnamate and butyl methoxydibenzoyl methane and a pharmaceutically acceptable vehicle, preferably a substantially alcoholic base.

According to yet another aspect of the invention there is provided a method of preparing a pharmaceutical composition for use in treating rosacea, erythemia, telangiectasia, and inflammatory lesions which method comprises incorporating an effective non-toxic amount of metronidazole as active ingredient in the composition together with an effective amount of at least one sunscreen

compatible with said effective non-toxic amount of metronidazole, preferably selected from the group consisting of octyl methoxy cinnamate and butyl methoxydibenzoyl methane and preferably in a pharmaceutically acceptable vehicle, preferably isopropyl alcohol.

According to yet another aspect of the invention there is provided the use of metronidazole, for the manufacture of a pharmaceutical composition or compositions for the medical treatment of acne and erythemia, telangiectasia, and inflammatory lesions associated with rosacea, characterized in that the composition or compositions are for use in humans for the treatment of acne and erythemia, telangiectasia, and inflammatory lesions, and the composition or compositions further comprise at least one sunscreen compatible with said metronidazole, preferably selected from the group consisting of octyl methoxy cinnamate and butyl methoxydibenzoyl methane and preferably in a pharmaceutically acceptable base for example gel base, preferably using isopropyl alconol.

According to yet another aspect of the invention there is provided the use of a non-toxic effective amount of metronidazole in combination with at least one sunscreen for the treatment of acne and erythemia, telangiectasia and inflammatory lesions associated with rosacea characterized by the use of a composition which comprises an effective non-toxic amount of metronidazole, an effective non-toxic amount of sunscreen compatible with said metronidazole and a compatible vehicle.

According to yet another aspect of the invention there is provided a topical pharmaceutical composition for the treatment of acne and rosacea, erythemia, telangiectasia, and inflammatory lesions associated with rosacea, characterized that said composition comprises an effective non-toxic amount of

metronidazole, an effective non-toxic amount of at least one sunscreen compatible with said metronidazole, where said composition is substantially non-stinging.

According to yet another aspect of the invention there is provided a topical pharmaceutical composition for the treatment of acne and rosacea, erythemia, telangiectasia and inflammatory lesions associated with rosacea, characterized that said composition comprises an effective non-toxic amount of metronidazole, an effective non-toxic amount of at least one sunscreen compatible where said composition is substantially preservative free.

In any of the above compositions, it is preferred that said compositions exhibit substantially at least one of the following characteristics:

(a) substantially non-stinging
(b) substantially non-burning
(c) substantially non-itching
and (d) substantially non-drying.

In any of the above, it is preferred that the sun protection factor (SPF) be at least 15.

The following example is illustrative of the manufacturing process used to prepare a 1.0% metronidazole gel with sunscreen.

Step A

In a suitable stainless steel container equipped with good agitation, charge

1) Isopropyl alcohol 99% USP 72.0250 kg

2)	Purified water USP	4.0 kg
3)	Dioctyl maleate MFR	5.0 kg
4)	Cyclomethicone NF	3.0 kg
5)	Octyl methoxy cinnamate MFR	7.8750 kg
6)	Isoarachidyl neopentanoate MFR	4.0 kg

and with stirring, warm to 50°C

Step B

To step A, add and stir until each is completely dissolved.

7)	Metronidazole USP	1.0 kg

then

8)	Butylmethoxybenzoylmethane MFR	2.0 kg

Step C

Start cooling the batch and in a sprinkling manner during a 5 minute period, add with good stirring.

9)	Hydroxypropyl cellulose NF	1.4 kg

Step D

Stir for an additional 10 minutes following the hydroxypropyl cellulose addition, allow the batch to stand overnight. (preferably >10 hours) and assure the container is well sealed.

Step E

Transfer into a holding tank or suitable containers and store in a quarantined area. Label with product name, lot number and quantity.

Step F

Calculate % yield, theoretical and actual, and advise Quality Control for sampling. Compositions having a concentration of metronidazole between 0.50% to 1.50% w/w were prepared in a similar manner with appropriate adjustments to the amount of Isopropyl alcohol 99% USP. The range being substantially 72.5250% - 71.5250 % w/w equating to 0.50% - 1.50% w/w of metronidazole respectively.

The following will provide as illustrative the clinical safety and efficacy of the topical metronidazole composition prepared according to an embodiment of the invention.

42 patients were initially entered in the study. 30 of them were included in the efficacy analysis for the entire duration of the study. All 42 patients were included in the safety analysis.

TABLE I PATIENTS EXCLUDED AT TIME OF WITHDRAWAL OR COMPLETELY EXCLUDED FROM THE EFFICACY ANALYSIS.

	PATIENT #	REASON
Completely excluded from efficacy analysis	1	-Failed to meet inclusion criteria No. 3
	17	-Withdrawn at Day 3 due to severe stinging
	34	-Patient on chronic steroid therapy
	35	-Withdrawn at Week 1 due to unspecified idiosyncratic papulopustular reaction
	39	-Patient on chronic steroid therapy
	40	-Inadequate washout period
Excluded at the time of withdrawal or protocol violation	13	-Unable to keep appointment after Week 3
	18	-Withdrawn after Week 9 due to a threatening heart attack
	28	-Took antibiotics after Week 3
	29	-Took antibiotics after Week 3
	33	-Patient voluntary withdrawal after Week 3
	49	-Took oral metronidazole after Week 3

Note: Patient #20 completed the study one week early (Week 11) to leave for vacation. This patient was nevertheless fully included in the efficacy analysis.

Study design:

Double-blind, placebo-controlled, randomized, split-face (paired) comparative trial.

Study medication:

1% metronidazole in an alcohol gel with sunscreens, made according to embodiment of invention.

Placebo: Alcohol gel with sunscreens, (made according to above embodiment of invention without metronidazole).

Duration of the study:

The patients were treated for nine weeks. Clinical evaluations were conducted at Week 3, 6 and 9. A follow-up evaluation was done at Week 12.

Diagnosis:

All the patients were diagnosed by the investigator as having rosacea. Each patient had a minimum of three papules and/or pustules on each side of the face, bilateral moderate to severe erythema and bilateral telangiectasia.

Patient demography:

Twenty-five women and seventeen men aged between 24 and 71 years participated in the trial.

Posology:

Application of gel occurred twice a day (morning and evening).

Criteria of effectiveness:

The primary efficacy variables were the papule and pustule counts and the severity of erythema and telangiectasia. These variables were measured at baseline and at the end of Weeks 3, 6 and 9 of the treatment. Then, following three weeks off medication (Week 12), these variables were once more evaluated.

RESULTS:

ASSESSMENT OF EFFICACY

Both forms of treatment, particularly the active group, decreased the total number of inflammatory lesions (papule and pustule). At the end of the treatment (Week 9), the total inflammatory lesion count, compared to baseline, was reduced by 62% with metronidazole and by 37% with the placebo (Table II).

After three weeks off from the therapy (Week 12), the total number of inflammatory lesions for both metronidazole and the placebo was still reduced compared to baseline (Table II).

TABLE II GROUP MEAN AND PERCENTAGE DECREASE FROM BASELINE FOR THE TOTAL INFLAMMATORY LESION COUNT WITH RESPECT TO TILE AND TREATMENT.

	Metronidazole		Placebo	
Time	Mean ± SE	% Decrease	Mean ± SE	% Decrease
Week 0	8.25 ± 0.79	N/A	7.83 ± 0.82	N/A
Week 3	5.44 ± 0.68	34.06	5.19 ± 0.74	33.72
Week 6	3.68 ± 0.71	55.39	4.61 ± 1.11	41.12
Week 9	3.16 ± 0.94	61.70	4.90 ± 1.45	37.42
Week 12	4.30 ± 0.92	47.88	5.10 ± 1.13	34.87

In order to minimize the effect of the variation in the number of inflammatory lesions at baseline observed among the patients, a statistical analysis was conducted on the group mean total inflammatory lesion count differences relative to baseline. The results of the statistical analysis, which are presented in Table III, demonstrate that both forms of treatment significantly decrease the total papule and pustule count and this for all time points of the study.

TABLE III GROUP MEAN TOTAL PAPULE AND PUSTULE COUNT DIFFERENCES RELATIVE TO BASELINE AND WITH RESPECT TO TIME AND TREATMENT.

	Metronidazole		Placebo		
Time	Mean ± SE	P Value[1]	Mean ± SE	P Value[1]	P Value[2]
Week 3	2.81 ± 0.70	0.0003	2.64 ± 0.69	0.0005	> 0.05
Week 6	4.90 ± 0.89	0.0001	3.71 ± 0.94	0.0004	> 0.05
Week 9	5.42 ± 0.96	0.0001	3.42 ± 1.22	0.0086	> 0.05
Week 12	4.43 ± 0.87	0.0001	3.33 ± 0.94	0.0013	> 0.05

[1] P value for comparison from baseline within treatment.

[2] P value for comparison between treatment.

As indicated in Tables IV to VII, the majority of patients did not experience stinging, burning, itching or dryness. The patients who did experience the above mentioned side effects reported them mostly as mild in nature. These sensations were of short duration and equally reported for both the placebo and the metronidazole. As the treatment progressed, the occurrence of these side effects were less frequent and were nearly absent by Week 12.

TABLE IV: INCIDENCE OF STINGING AT EACH VISIT

WEEK 3

	Absent	Mild	Moderate	Severe
METRONIDAZOLE GEL (n=41)	22(53.7%)	14(34.2%)	4(9.8%)	1(2.4%)
PLACEBO (n=41)	23(56.1%)	13(31.7%)	4(9.8%)	1(2.4%)

WEEK 6

	Absent	Mild	Moderate	Severe
METRONIDAZOLE GEL (n=36)	27(75.0%)	7(19.4%)	2(5.6%)	0
PLACEBO (n=36)	24(66.7%)	10(27.8%)	2(5.6%)	0

WEEK 9

	Absent	Mild	Moderate	Severe
METRONIDAZOLE GEL (n=36)	25(69.4%)	10(27.8%)	1(2.8%)	0
PLACEBO (n=36)	25(69.4%)	9(25.0%)	2(5.6%)	0

WEEK 12 (POST TREATMENT)

	Absent	Mild	Moderate	Severe
METRONIDAZOLE GEL (n=35)	34(97.1%)	1(2.9%)	0	0
PLACEBO (n=35)	35(100.0%)	0	0	0

TABLE V: INCIDENCE OF BURNING AT EACH VISIT.

WEEK 3

	Absent	Mild	Moderate	Severe
METRONIDAZOLE GEL (n=41)	30(73.2%)	8(19.5%)	3(7.3%)	0
PLACEBO (n=41)	29(70.7%)	8(19.5%)	3(7.3%)	1(2.4%)

WEEK 6

	Absent	Mild	Moderate	Severe
METRONIDAZOLE GEL (n=36)	26(72.2%)	10(27.8%)	0	0
PLACEBO (n=36)	26(72.2%)	9(25.0%)	1(2.8%)	0

WEEK 9

	Absent	Mild	Moderate	Severe
METRONIDAZOLE GEL (n=36)	30(83.3%)	6(16.7%)	0	0
PLACEBO (n=36)	31(86.1%)	4(11.1%)	1(2.8%)	0

WEEK 12 (POST TREATMENT)

	Absent	Mild	Moderate	Severe
METRONIDAZOLE GEL (n=35)	35(100.0%)	0	0	0
PLACEBO (n=35)	34(97.1%)	1(2.9%)	0	0

TABLE VI: INCIDENCE OF ITCHING AT EACH VISIT.

WEEK 3

	Absent	Mild	Moderate	Severe

METRONIDAZOLE GEL (n=41)	28(66.3%)	10(24.4%)	3(7.3%)	0
PLACEBO (n=41)	26(68.3%)	10(24.4%)	3(7.3%)	0

WEEK 6

	Absent	Mild	Moderate	Severe
METRONIDAZOLE GEL (n=36)	28(77.8%)	8(22.2%)	0	0
PLACEBO (n=36)	27(75.0%)	9(25.0%)	0	0

WEEK 9

	Absent	Mild	Moderate	Severe
METRONIDAZOLE GEL (n=36)	31(86.1%)	5(13.9%)	0	0
PLACEBO (n=36)	30(83.3%)	6(16.7%)	0	0

WEEK 12 (POST TREATMENT)

	Absent	Mild	Moderate	Severe
METRONIDAZOLE GEL (n=35)	34(97.1%)	0	1(2.9%)	0
PLACEBO (n=35)	34(97.1%)	0	1(2.9%)	0

TABLE VII: INCIDENCE OF DRYNESS AT EACH VISIT.

WEEK 3

	Absent	Mild	Moderate	Severe
METRONIDAZOLE GEL (n=41)	23(56.1%)	10(24.4%)	8(19.5%)	0
PLACEBO (n=41)	20(48.8%)	15(36.6%)	6(14.6%)	0

WEEK 6

	Absent	Mild	Moderate	Severe
METRONIDAZOLE GEL (n=36)	26(72.2%)	8(22.2%)	2(5.6%)	0
PLACEBO (n=36)	26(72.2%)	8(22.2%)	2(5.6%)	0

WEEK 9

	Absent	Mild	Moderate	Severe
METRONIDAZOLE GEL (n=36)	24(66.7%)	11(30.6%)	1(2.8%)	0
PLACEBO (n=36)	22(61.1%)	13(36.1%)	1(2.8%)	0

WEEK 12 (POST TREATMENT)

	Absent	Mild	Moderate	Severe
METRONIDAZOLE GEL (n=35)	32)91.4%)	2(5.7%)	1(2.9%)	0
PLACEBO (n=35)	30(85.7%)	4(11.4%)	1(2.9%)	0

The results showed that, compared to baseline, metronidazole 1% gel with sunscreen is effective in significantly decreasing the number of inflammatory lesions and the level of erythema and telangiectasia associated with rosacea. From the point of safety, most patients did not report side effects.

In conclusion, this study showed evidence of a beneficial effect on the natural course of rosacea from the topical application of Metronidazole 1% gel.

The following also provide examples of formulations for metronidazole gel 0.50% w/w and 1.50% w/w, respectively.

METRONIDAZOLE GEL 0.5% WITH SUNSCREEN

MANUFACTURING FORMULA FOR **100.0000 kg**

1	Isopropyl alcohol 99% USP	72.5250	72.5250
2	Purified Water USP	3.6000	3.6000
3	Dioctyl Maleate MFR	5.0000	5.0000
4	Cyclomethicone NF	3.0000	3.0000
5	Octylmethoxy cinnamate MFR (Parsol MCX MFR)	7.5	7.5
6	Isoarachidyl neopentanoate MFR (Elefac I-205 MFR)	4.0000	4.0000
7	Metronidazole USP	0.5000	0.5000
8	Butylmethoxybenzoyl methane MFR (Parsol 1789 MFR)	2.0	2.0
9	Hydroxypropyl cellulose NF	1.4000	1.4000
	TOTAL	**100.0000**	**100.000**

METRONIDAZOLE GEL 1.5% WITH SUNSCREEN

MANUFACTURING FORMULA FOR 100.0000 kg

1	Isopropyl alcohol 99% USP	71.5250	71.5250
2	Purified Water USP	3.6000	3.6000
3	Dioctyl Maleate MFR	5.0000	5.0000
4	Cyclomethicone NF	3.0000	3.0000
5	Octylmethoxy cinnamate MFR (Parsol MCX MFR)	7.5	7.5
6	Isoarachidyl neopentanoate MFR (Elefac I-205 MFR)	4.0000	4.0000
7	Metronidazole USP	1.5000	1.5000
8	Butylmethoxybenzoyl methane MFR (Parsol 1789 MFR)	2.0	2.0
9	Hydroxypropyl cellulose NF	1.4000	1.4000
	TOTAL	100.0000	100.000

Although Parsols were described in the preferred embodiment of the inventions as the sunscreens, other compatible sunscreens can be used. Parsols are preferred due to their substantially non-sensitizing characteristics as opposed to PABA and it's ester derivatives that have been demonstrated to cause contact and photo contact sensitization in treated subjects.

As many changes can be made to the examples and embodiments described herein without departing from the scope of the invention, it is intended that all material contained herein be interpreted as illustrative of the invention and not in a limiting sense.

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE AS FOLLOWS:

1. A topical composition for the treatment of rosacea and acne comprising:
   (a) an effective amount of metronidazole or salt thereof;
   (b) an effective amount of at least one sunscreen compatible with said metronidazole;
   (c) a substantially alcoholic base as a vehicle.

2. In the treatment of rosacea and acne a topical composition comprising:
   (a) an effective amount of metronidazole or salt thereof;
   (b) an effective amount of at least one sunscreen compatible with said metronidazole; and
   (c) a pharmaceutically acceptable vehicle.

3. A method of treating rosacea and acne comprising the topical application of an effective amount of metronidazole in combination with an effective amount of at least one sunscreen compatible with said metronidazole and a pharmaceutically acceptable alcoholic base.

4. A composition for the treatment of rosacea and acne comprising:
   (a) an effective amount of isopropyl alcohol 99% USP
   (b) an effective amount of purified water USP
   (c) an effective amount of dioctyl maleate MFR
   (d) an effective amount of cyclomethicone NF
   (e) an effective amount of Octyl Methoxycinnamate

(f) an effective amount of Isoarachidyl neopentanoate MFR

(g) an effective amount of metronidazole USP

(h) an effective amount of Butyl Methoxybenzoyl methane and

(i) an effective amount of hydroxypropyl cellulose NF

5. The composition of Claim 1 further comprising an effective amount of an emollient.

6. The composition of Claim 1 further comprising an effective amount of lubricating agent.

7. The composition of Claim 2 where said pharmaceutically acceptable vehicle is an alcoholic gel base.

8. The composition of Claim 1 where said at least one sunscreen is selected from Octyl Methoxycinnamate and Butyl Methoxybenzoylmethane.

9. The composition of Claim 5 where said at least one emollient is selected from dioctyl maleate MFR and Isoarachidyl Neopentanoate MFR.

10. The composition of Claim 6 where said lubricating agent is selected from cyclomethicone NF.

11. The composition of Claim 1 further comprising an effective amount at least one gelling agent.

12. The composition of Claim 11 where said gelling agent is hydroxypropyl cellulose NF.

13. A topical composition for the treatment of rosacea and acne comprising:

(a) an effective amount of an antibiotic;

(b) an effective amount of a sunscreen;

(c) an effective amount of an emollient;

(d) an effective amount of a lubricant;

(e) an effective amount of a gelling agent; and

(f) an effective amount of a pharmaceutically acceptable diluent or carrier for the above.

14. A substantially topical anhydrous composition for the treatment of rosacea comprising:

(a) an effective non-toxic amount of an antibiotic;

(b) an effective non-toxic amount of a sunscreen;

(c) an effective non-toxic amount of an emollient;

(d) an effective non-toxic amount of a lubricant;

(e) an effective non-toxic amount of a gelling agent; and

(f) an effective amount of a pharmaceutically acceptable diluent or carrier.

15. The composition of Claim 13 or 14 wherein said antibiotic is an effective non-toxic amount of metronidazole.

16. The composition of Claim 13 or 14 wherein said sunscreen is selected from the group Octyl Methoxycinnamate and Butyl Methoxydibenzoyl methane.

17. The composition of Claim 13 or 14 wherein said emollient is selected

from the group dioctyl maleate MFR and isoarachidyl neopentanoate MFR.

18. The composition of Claim 13 or 14 wherein said lubricant is cyclomethicone NF.

19. The composition of Claim 13 or 14 wherein said gelling agent is hydroxypropylcellulose NF.

20. The composition of Claim 13 or 14 wherein said pharmaceutically acceptable carrier or diluent is isopropyl alcohol 99% USP.

21. The composition of Claim 13 or 14 further being substantially preservative-free.

22. A method of preparing a pharmaceutical composition for use in treating rosacea, erythemia, telangiectasia, and inflammatory lesions which method comprises incorporating an effective non-toxic amount of metronidazole as active ingredient in the composition together with an effective amount of at least one sunscreen compatible with said effective non-toxic amount of metronidazole, and a substantially alcoholic base as a vehicle.

23. The use of metronidazole and a compatible sunscreen, for the manufacture of a pharmaceutical composition or compositions for the medical treatment of acne and erythemia, telangiectasia, and inflammatory lesions associated with rosacea, characterized in that the composition or compositions are for use in humans for the treatment of acne and erythemia, telangiectasia, and inflammatory lesions, and the composition or compositions further comprise at least one sunscreen compatible with said metronidazole, and a substantially alcoholic base.

24. The method of claim 22 wherein said effective amount of at least one sunscreen is selected from the group Octyl Methoxycinnamate and Butyl Methoxydibenzoyl methane.

25. The use of claim 23, wherein said at least one sunscreen is selected from the group Octyl Methoxy cinnamate and Butyl Methoxy dibenzoyl methane.

26. A topical composition for the treatment of rosacea, erythemia, telangiectasia, and inflammatory lesions associated with rosacea, erythemia, telangiectasia, said topical composition comprising:

a) isopropyl alcohol 99% USP in the amount of about 72.5% - 71.5% w/w

b) purified waterUSP in the amount of about 4.0% w/w

c) dioctyl maleate MFR in the amount of about 4.85%-5.5% w/w

d) cyclomethicone NF in the amount of about 2.91%-3.5% w/w

e) Octyl Methoxycinnamate in the amount of about 7.5%-8.0% w/w

f) isoarachidyl neopentanoate MFR in the amount of about 3.75%-4.5% w/w

g) metronidazole USP in the amount of about 0.50% - 1.50% w/w

h) Butyl Methoxydibenzoyl methane in the amount of about 2.0%-2.2% w/w and

i) hydroxypropyl cellulose NF in the amount of about 1.2%-1.5% w/w, or pharmaceutically acceptable chemical equivalents of each of a)-i).

27. The use of metronidazole and compatible sunscreen for the treatment of acne and erythemia, telangiectasia and inflammatory lesions associated with rosacea characterized by the use of a composition which comprises an effective amount of metronidazole, an effective amount of sunscreen compatible with the

metronidazole and a compatible vehicle.

28. The use of claim 27 wherein the vehicle is a substantially alcoholic base.

29. The use of claims 27 or 28 wherein the sunscreen is selected from Octyl Methoxycinnamate and Butyl Methoxy dibenzoyl methane.

30. The composition of any of claims 1,2,4,5,6,8,13,14,15 and 26 wherein said composition is in the form of a substantially alcoholic base gel.

31. The use of Metronidazole and compatible sunscreen for the reduction and/or management of conditions associated with rosacea, where said metrodinazole is used in combination with at least one compatible sunscreen, where said metronidazole and said at least one compatible sunscreen are in association with a pharmaceutical acceptable gel base.

32. The composition of claim 1, 4, 13, 14 or 26 wherein said composition further comprises at least one of the following characteristics:

(a) substantially non-stinging
(b) substantially non-burning
(c) substantially non-itching
and (d) substantially non-drying.

33. The use of claim 31 wherein said gel base is substantially alcoholic.

34. The composition of claim 1, 4, 13, 14 and 26 wherein said composition has a minimum SPF of 15.